Factors Which Affect Adherence to Antiretroviral Medications in a Cohort of HIV-Positive VA Patients

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The introduction of highly active antiretroviral therapy (HAART) regimens has improved the virologic, immunologic, and clinical outcomes of HIV infection.(1) Nonadherence to medications, however, remains a major obstacle to successful medical treatment. Despite the efforts of providers and health systems to encourage adherence, irregular and incomplete drug dosing is common. The economic burden of medication nonadherence, combining both direct and indirect costs, is estimated to be as high as $100 billion annually.(2) Failure to adhere to prescribed HIV therapy may result in treatment failure as drug-resistant strains produce elevated viral loads and disease progression.

Although treatment adherence does not guarantee successful clinical outcome, and suboptimal adherence does not always lead to virologic failure, it is generally accepted that patients who do not adhere to their antiretroviral regimen (ie, at least 90-95% of prescribed doses taken) are at a higher risk for adverse virologic and clinical outcomes.(1,2,3) Many studies have demonstrated that adherence rates of 95% or greater optimize virologic and clinical outcomes (decreased opportunistic infections, increased CD4 count).(1,2,4,5)

Nonadherence to antiretroviral therapy occurs for many reasons. Studies have examined the degree to which variables, such as health beliefs, psychiatric beliefs, substance abuse, adverse events from therapy, cognitive functioning, and demographic characteristics, might be associated with medication adherence among HIV-infected patients.(1,5,6,7) Individual drugs differ in taste, size, pill burden, and dosing frequency requirements. The purpose of this study is to investigate whether specific antiretroviral medications are associated with greater adherence.

METHODS

We performed a one-year retrospective outpatient chart review of 161 HIV-positive patients at the Charleston, South Carolina VA Medical Center (VAMC). The primary endpoint of this study was to investigate whether specific antiretroviral medications were associated with an increased rate of adherence. As a secondary objective, we sought to determine the relationship between adherence, viral suppression, and common confounders in HIV-positive patients such as hepatitis C coinfection, pill burden, frequency of dosing, CD4 count, and antiretroviral treatment status (naïve vs. experienced).

Patients were included in the study based on the following criteria: 1) Enrolled in the Infectious Disease clinic at the Charleston VAMC during the study period; 2) Had an active prescription for any antiretroviral medication at the Charleston VAMC; 3) Antiretroviral medications were filled by the Charleston VAMC pharmacy; and 4) Lab tests were performed at the Charleston VAMC laboratories. Medication refill histories were based on the VAMC computerized record system. A Medication Possession Ratio (MPR) was calculated for each patient (number of days dispensed/average days between refills). This number was then averaged for all patients who were taking that particular drug. This average MPR was used as a primary endpoint of adherence. Prior to review, we defined high adherence as an MPR value of >=0.95. This number is equivalent to a 95% adherence rate, which earlier studies have determined is needed for optimal treatment.(3) The association between adherence and frequency of dosing, hepatitis C status, HIV viral load, antiretroviral treatment status, CD4 count at the beginning of the study period, and pill burden was also assessed using the χ^2 test and logistic regression. The average MPR of each patient's entire HAART regimen was used in these calculations. We received expedited IRB and R&D approval from the Medical University of South Carolina and the Charleston VAMC.

RESULTS

Baseline Characteristics

The average age of patients reviewed during the study period was 51.2 years. The average CD4 count at baseline was found to be 435 cells/µL. This correlates with a low percentage (24%) of patients with CD4 counts <200 cells/µL, which is one characteristic that defines active AIDS. Table 1 provides all other baseline characteristics which were assessed.

TABLE 1 – Baseline Characteristics

Characteristic	No. of Patients (%) N=161
Hepatitis C Negative*	118 (75%)
Antiretroviral Experienced	99 (61%)
Frequency >1 time/day	145 (90%)
CD4 <= 200 cells/µL	38 (24%)
MPR >= 0.95	71 (44%)
Viral Load <= 50 copies/mL**	90 (58%)

*3 patients with unknown status
**6 patients with unknown status

Primary Endpoint

Of the 21 medications assessed, 7 were associated with high adherence (Tables 2 and 3). Based on an analysis of drug characteristics (frequency of dosing and number of tablets), we found no similarities in the 7 medications versus those in the lower adherence group. However, since the average MPR is based on the number of patients taking each particular medication, the larger the number of patients taking the drug, the stronger the value of the association. An MPR based on drugs taken by <10 patients, may lack the power to demonstrate a strong correlation with adherence. Future investigation may include adverse effects, tablet characteristics, timing of administration, storage, and patient perception of the different medications.

TABLE 2 – High Adherence Medications (MPR ≥ 0.95)

Medication	# of Patients	MPR
Didanosine 250 mg	11	1.35
Boosted Atazanavir	10	1.24
Nevirapine	21	1.01
Boosted Indinavir	7	0.99
Trizivir	24	0.98
Boosted Fosamprenavir	3	0.97
Tenofovir	37	0.97

TABLE 3 – Medications with MPR value < 0.95

Medication	# of Patients	MPR
Lamivudine 300 mg	12	0.93
Nelfinavir	18	0.91
Efavirenz	67	0.89
Combivir	62	0.88
Stavudine	29	0.87
Atazanavir	5	0.87
Didanosine 400 mg	18	0.84

Boosted Amprenavir	2	0.83
Abacavir	19	0.80
Lamivudine 150 mg	30	0.80
Kaletra	32	0.79
Zidovudine	4	0.79
Indinavir	10	0.72
Amprenavir	3	0.67

Secondary Endpoints

As a secondary endpoint, we determined the relationship between high adherence and viral suppression. Earlier studies have shown a direct relationship in that patients with high adherence are more likely to have a suppressed virus.(5,7) In this study, we did find a significant relationship as well between these characteristics (Figure 1). Of the patients who were classified as high adherence based on their MPR value, 69% also had a suppressed virus; compared with only 49% of patients with an MPR value <0.95 (OR 2.26; 95% CI 0.07 to 0.76). We defined viral suppression for the purpose of this study as a viral load <50 copies/mL for >=50% of the study period with their most recent viral load remaining <50 copies/mL. We also found that viral suppression was more likely to occur in patients who were antiretroviral naïve prior to the study period (OR 2.29; 95% CI 0.04 to 0.81) and those with CD4 counts >200 cells/µL (OR 2.75; 95% CI 0.10 to 0.93).

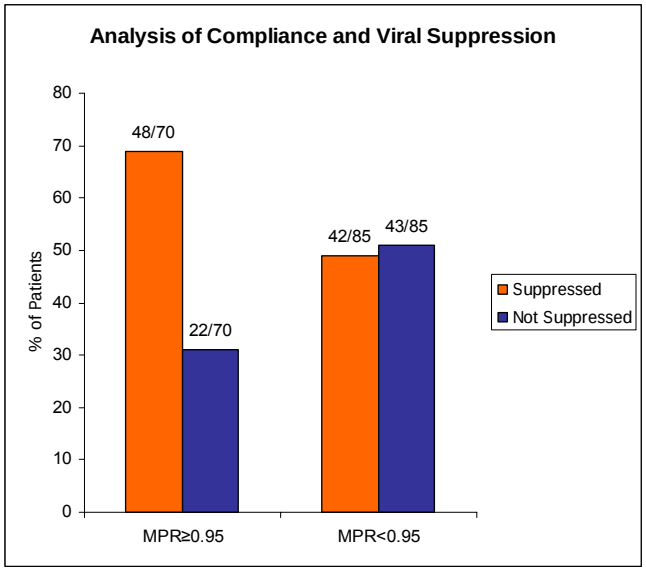

FIGURE 1 – Viral Suppression and Compliance

As another secondary endpoint, we determined the relationship between high adherence and common confounders of HIV patients. We did find a trend in patients coinfected with hepatitis C being more likely to be nonadherent, however this difference was not statistically significant (p=0.0643). Earlier studies have shown that coinfected patients are more likely to be nonadherent, which this study also suggests.(8)

We also analyzed the relationship between common confounders in HIV patients and their role in adherence. No significant relationship was found between antiretroviral status prior to the study period (p=0.4176), frequency of dosing (p=0.7916), CD4+ count (p=0.7114), overall pill burden (p=0.8741), or antiretroviral pill burden (p=0.2033) and adherence.

DISCUSSION

Seven medications (of 21 studied) were associated with an increased rate of adherence at the Charleston VAMC. However, no correlation was found between these medications upon initial examination of number of tablets and frequency of dosing. Adherence was evaluated using the average MPR for each medication based on the patients taking a particular medication. Because of this, some medications may have had very few patients receiving the medication during the study period, limiting the statistical power to determine the relationship between pill burden and adherence. Therefore, some medications may seem to be associated with high adherence (ie, boosted indinavir and fosamprenavir) or low adherence, which may not truly be the case. Therefore, further investigation needs to occur with a larger patient population and a longer study period in order to completely determine this relationship.

There was a trend towards patients coinfected with hepatitis C being less likely to adhere to their antiretroviral regimens, which is consistent with prior studies.(8) No other confounders that were analyzed seemed to have a role in adherence in this patient population. Many studies have shown the benefit of once-daily dosing in the HIV population as well as other chronic disease states in which patients are prescribed multiple medications.(5,6,7) We expected to see this correlation as well; however, at the time of this study (2003-2004) only ~10% of the patients were on once-daily HAART regimens. We suspect that there will be a larger correlation between once-daily dosing and adherence if this study is pursued further due to the tremendous efforts by pharmaceutical companies to decrease the frequency of dosing and pill burden of all antiretrovirals.

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